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TITLE: The Impact of Risk Factors and Genetic Polymorphism in Metabolic Enzymes on Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers and Non-Mutation Carriers

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13. ABSTRACT ***(Maximum 200 Words)***

One mutation in each BRCA gene, a BRCA2 founder mutation and a rare BRCA1 mutation account for most familial breast cancer in a well defined population. Our previous studies show that the penetrance of the BRCA2 mutation varies greatly, suggesting the involvement of modifying factors, genetic and/or environmental.

The study group consists of all women in Iceland who have had breast cancer and are alive at the time of study, their female relatives and age matched controls, estimated 5000 women.

Hypotheses tested are that environmental risk factors and genetic variation in metabolic enzymes affect,

1. Penetrance of BRCA mutations
2. Breast cancer risk in the population

Hypothesis 1. is studied in women with breast cancer who have a BRCA mutation and mutation carrier relatives without breast cancer. Comparison group are women with breast cancer without BRCA mutations and unaffected mutation negative relatives. Risk factors investigated: Reproductive factors, ionizing radiation, physical exercise, alcohol use, smoking, height and weight. The enzymes investigated affect levels of sex hormones and formation of carcinogenic substances. 2. is studied in 1200 women with breast cancer, representative for breast cancer patients in the population, and 1200 age-matched controls without breast cancer, representative for women without breast cancer.

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4. INTRODUCTION

This is a population based study on the effects of environmental factors and polymorphism in metabolic enzymes on breast cancer risk in BRCA1 and BRCA2 mutation carriers and non-mutation carriers. The purpose is to test whether environmental risk factors and genetic variation in metabolic enzymes affect penetrance of BRCA mutations and breast cancer risk in the population in general. The aim is to include all Icelandic women who have been diagnosed with breast cancer and their first degree relatives as well as an age-matched comparison group.

5. BODY

Task 1 *(Preparation for recruitment,)* Months 1-3.

- Media announcements were prepared.
- Notice was designed to be distributed to community health centres.
- Plan for contacting "Reach to Recovery" was designed.
- Telephone answering service for the study was set up at the Cancer Society in May 1999.
- A computer programme for registration of participants was developed.
- A computer programme for entering answers to questionnaires was developed.

Task 2 *(Recruitment first round),* Months 3-9.

- In order to introduce the study to women with breast cancer we gave a two page interview in Morgunbladid (the most widely read daily newspaper in Iceland) May 9th 1999 (see attached copy of the interview).
- May 10th 1999 we sent an invitation to participate in our study along with a circular letter from the organisers of the Icelandic "Reach to Recovery" group to their members (500 women). The women were asked to contact us by telephone if they were interested in participating.
- Lecture and discussion at a meeting of the "Reach to Recovery" group (JEE, LT).
- Lectures and discussions at evening meetings of local cancer societies in two country areas (east and south) in autumn 1999 and spring 2000 (JEE).
- A deviation from the recruitment plan was that we have not yet contacted Community Health Centres. The reasons for this relate to increased interest in cancer research in Iceland by clinicians and biotechnological companies. Surgical and medical oncologists have formed a new working group, the Icelandic Breast Cancer Group (IBCG) that wants to be actively involved in all breast cancer research in Iceland. The IBCG requested that our study was put on hold while negotiations on possible collaborations were taking place (see accompanying letter).
- The initial response to the "Reach to Recovery" letter was 32%, with phonecalls received from 162 women diagnosed with breast cancer. They were given appointments and questionnaires sent to them. No follow-up has yet been done, for the above mentioned reasons.

Task 3 *(Collection of data and blood samples),* Months 5-41.

- Data and blood samples have been collected from the 162 women and 417 of their female relatives as well as from 82 age-matched controls from the Cancer Detection Clinic. The answers to the questionnaires have been entered into a databank. The blood samples were frozen at –80°C within an hour of collection and processed in batches, see Task 6.

Task 4 *(Preparation of recruitment, second round)* Months 5-36.

- The 162 women constitute 11% of the 1461 women diagnosed with breast cancer and living in Iceland at the end of 1999 according to the Icelandic Cancer Registry.
- It was planned to send out further letters in collaboration with the "Reach to Recovery" group and also to contact women who had breast cancer diagnosis via the local cancer societies around Iceland. It was further in our plan to contact the then remaining women registered in the population-based Cancer Registry with breast cancer, via their doctors.
- As described above, this plan had to be put on hold. After several months of negotiations with the IBCG we have now reached an agreement and will be able to go ahead as planned. These problems have been costly for us in terms of wasted manpower and time. The agreement with IBCG should, however, strengthen our study. As an example, we now expect to be able to recruit a control group based on the entire population of Icelandic women instead of limiting our control group to women attending the Cancer Detection Clinic.

Task 5 *(Recruitment, second round),* Months 15-30.
Not applicable in this report.

Task 6 *(Processing and storage of samples),* Months 5-36.
This task has proceeded according to plan. DNA has been prepared from the samples in batches using the classical phenol/chloroform extraction method. About 80% of samples collected so far have been processed.

Task 7 *(Laboratory analysis),* Months 10-48.
Analysis of mutations and genetic polymorphisms is in progress as planned. Measurement of serum hormone levels will not be included in this sudy, according to reccomendations from reviewers.

Task 8 *(Statistical analysis),* Months 49-60.
Not applicable in this report

6. KEY RESEARCH ACCOMPLISHMENTS

None at this stage.

7. REPORTABLE OUTCOMES

- Manuscripts, abstracts, presentations

- Lecture at a meeting of the "Reach to Recovery" group (JEE, LT).
- Lectures at evening meetings of local cancer societies in two country areas (east and south) in autumn 1999 and spring 2000 (JEE).
- Presentation at a meeting of the Association of Nordic Cancer Registries (ANCR) in Stockholm, Oct. 27. 1999. Title: Assembling a group for studying breast cancer, risk factors, BRCA mutations and genetic polymorphism in metabolic enzymes.
- A poster presented at the Icelandic Biology Society Colloquium November 1999. Title: The Impact of Risk Factors and Genetic Polymorphism in Metabolic Enzymes on Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers and Non-Mutation Carriers. An introduction of a new population-based study.
- A poster presented at a breast cancer conference of the Icelandic Association of Cancer Research Jan. 22. 2000. Title: A Population based study on the Impact of Risk Factors and Genetic Polymorphism in Metabolic Enzymes on Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers and Non-Mutation Carriers.

- Degrees obtained that are supported by this award

- Standardization of methods for assessment of genetic polymorphisms in metabolic enzyme genes and determination of allele frequencies in the Icelandic population as part of a MSc project completed summer 2000.

- Informatics and databases

- A database of participants.
- A database of answers to questionnaires.

- Funding applied for based on work supported by this award

- A grant has been awarded by the Icelandic Science Foundation for a study on Nutrition, DNA adducts and DNA repair in breast cancer, in collaboration with our group.

- Employment and research opportunities applied for and/or received on experiences/training supported by this award

- The IBCG has developed a protocol in collaboration with our group and an Icelandic biotechnological company, UVS Icelandic Genomics. This includes clinical, SNP's and gene expression studies on breast cancer.

8. CONCLUSIONS

We have had very positive response from Icelandic women in connection with this study, who have repeatedly expressed interest in our approach. The delay in recruitment is due to reasons related to negotiations with IBCG as detailed above.

9. REFERENCES

None at this stage

10. APPENDICES

Accompanying letter

Commander
U.S. Army Medical Research and Material Command
ATTN: MCMR-RMI-S
504 Scott Street
Fort Detrick, Maryland 21702-5012

Icelandic Cancer Society

September 26th 2000

Concerning Award Number: **DAMD17-99-1-9216**

Dear Sir/Madame,

As described in our report, the initial recruitment effort for this study was successful. It was undertaken in collaboration with the breast cancer patient support group, equivalent of the "Reach to Recovery" group in the USA, as planned in our project protocol inviting women to participate in the study. Women met the study with interest. Our recruitment plan, however, was put to a halt earlier this year. The reasons for this relate to increased interest in cancer research in Iceland by clinicians and biotechnological companies. Surgical and medical oncologists have formed a new working group, the Icelandic Breast Cancer Group (IBCG), that wants to be actively involved in all breast cancer research in Iceland. The IBCG requested that our study be put on hold while negotiations on possible collaborations were taking place.

We have had negotiations with the IBCG for several months and have now reached an agreement and will be able to go ahead as planned. This has been costly for us in terms of wasted manpower and time. In spite of the slowing down of recruitment and sample collection our expenses have not been significantly reduced. Specialised staff had been hired for this project and their salaries had to be paid. The present agreement* with the IBCG should, however, strengthen our study in the long run. As an example, we now expect to be able to recruit a control group based on the entire population of Icelandic women instead of limiting our control group to women attending the Cancer Detection Clinic. It is also very important for our study to have the support and co-operation of local cancer specialists.

* The agreement with the IBCG involves joint recruitment of patients, former patients and controls for our study and a different study of the IBCG in collaboration with an Icelandic biotech company, Icelandic Genomics, UVS.

We hope that these unusual circumstances will be taken into consideration in the evaluation of our report.

Sincerely,

J. E. Eyfjörð

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